A Thesis for the degree of Doctor of Medicine in the University of Edinburgh

presented by

Patrick Stevenson Haldane.

"On the Diagnosis of Diseases of the Pancreas with Special Reference to the So-called "Pancreatic Reaction"

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Patrick Stevenson Haldane, M.B., Ch.B. April 1905.

The study of affections of the pancreas is one which has largely developed within the last ten years. If one refers to such a well-known and comprehensive text book as that of Hilton Fagge & Pye-Smith in its second edition dated 1888,- (only about 15 years ago) we find that barely a page and a half is directed to this special subject, out of a total text of some 1800 pages. If, on the other hand, we consult some recent books, we get an indication of the progress of study and interest in this field. In the Text Book of Medicine edited by G.A. Gibson (1901) we find seven large pages allotted to this topic; in Osler's Principles and Practice of Medicine, 4th. edition, 1901, there are eight pages of somewhat condensed writing; in Quain's Dictionary of Medicine, 3rd. edition, 1901, there are nine full pages in double column devoted exclusively to the pancreas; while in Clifford Allbutt's exhaustive System of Medicine, we find in Volume IV, (1897) no fewer than sixteen pages dealing with this special subject.

No doubt one of the reasons for this increase in interest and in knowledge of the diseases of this

organ is to be found in the great increase in abdominal operations during the past ten or fifteen years. Many sections done on obscure abdominal cases must have revealed lesions of the pancreas which were not recognized. In this way a considerable amount of knowledge was built up, and definite clinical entities established, and only after a large number of such sections did it become possible to classify the affections of the gland, on a sure basis, and to correlate with each ~~other~~ its proper symptomatology. No doubt post-mortem observations would have contributed largely to the knowledge of the earlier writers, but by that time the case was ended and further clinical data rendered impossible, which was not the case with surgical interference whether that proved directly successful or not. The natural deep position of the organ too, rendered the diagnosis of its diseases difficult, and this leads one to a short consideration of the anatomy of the gland, based upon some of the most modern investigations.

Anatomy of the Pancreas.

The normal pancreas is an elongated, irregularly shaped gland, consisting of a head, body and tail. The size and shape vary greatly, its length being from 12-20 cm., and its weight 80-88 grms. The greater part of the gland lies in the epigastric region, while a small part of the body and the tail extend into the left hypochondrium. Its head lies in the concavity of the duodenum, and comes into re-

relationship with the inferior vena cava, and the aorta behind, and is expanded and bulbous. The anterior surface comes in contact, above, with the transverse colon without intervention of peritoneum, and below is invested by peritoneum in which lies the small intestine. The neck is a constricted part of the gland, connected with the upper and anterior part of the head, and along this constriction run the superior mesenteric vessels. The pancreatico-duodenal vessels on the other hand descend and break up on the anterior aspect of the head. The portal vein comes into relation with the posterior aspect of the neck, and is formed by the union of splenic and superior mesenteric veins at its lower border. We thus see the intimate relation existing between the gland and many large arteries and veins and, no doubt, constituting a means of physiological and pathological alteration in the organ. The body is approximately prismatic in shape, presenting three faces,- superior, inferior and posterior. It (the body) runs back and to the left, being related to the left kidney and suprarenal capsule behind, and the stomach in front, and can thus be exposed by cutting through the greater omentum and throwing the stomach upwards. The body ends in a tapering part,- the tail, which reaches to the concavity of the spleen; no line determines the junction of body and tail. It is worth noting that the posterior surface of the body is not clothed by peritoneum, being connected to

the posterior abdominal wall by areolar tissue. The vascular supply is rich and comes from four main sources, viz:- (1) the superior pancreatico-duodenal, a branch of the gastro-duodenal; (2) the inferior pancreatico-duodenal and the inferior pancreatic springing from the superior mesenteric ; (3) the splenic artery with its pancreatic branches; and (4) twigs from the hepatic artery. The veins are the anterior pancreatico-duodenal (joining the superior mesenteric vein) and the posterior pancreatico-duodenal opening into the portal; there are also several small tributaries entering the splenic vein as it runs from left to right. Some tributaries from the neck join the portal vein direct, which finally receives all the venous blood from the organ. The lymphatics all join the coeliac plexus of glands. The nerves, which are almost all non-medullated, come through coeliac, splenic, and superior mesenteric plexuses, from the solar plexus. The ducts have been left over to the section dealing with the physiology of the organ, as alterations in them constitute an important factor in the pathological changes in the gland. The above is based largely on the article by Ambrose Birmingham in Cunningham's Text-Book of Anatomy (1902) and Opie's Disease of the Pancreas (1903).

The Physiology of the Pancreas.

The pancreas is a racemose tubular gland, and, closely resembles the salivary glands, being however

much more complex in nature. In general it may be said that it consists of branching and subdividing tubules opening eventually into gland acini. The larger ducts are lined by columnar epithelial cells, the smaller by cubical ones, eventually becoming flattened. The acini or secreting parts proper are lined by polygonal characteristic granular cells, the granules lying in that part of the cell next the lumen, while the outer zone is clear. During secretion, these zymogen granules are discharged, the clear part thus growing wider. These granules are believed to represent a substance called trypsinogen, the precursor of tyypsin. This tubulo-racemose portion lies in a loose matrix of connective tissue. In addition to the ordinary secreting portion of the gland, there are groups or islands of cells, described by Langerhans, and lying in the centre of the acini. These islands may consist of only two or three cells, which have a spindle-shape, are somewhat flattened, and resemble the lining cells of the smaller ducts. To these cells Langerhans gave the name of centro-acinar. The exact nature of those cells is unknown, although many observers have regarded tham as analogous to lymph-follicles, and much interest has been aroused in reference to them owing to the fact that degenerative changes in them were frequently associated with the occurrence of glycosuria, and that in fat necrosis of the pancreas they are the only cells which remain. They occur in

the pancreas of all vertebrates. Through the courtesy of Dr. Anderson, Pathologist to the Victoria Infirmary, Glasgow, I have had the opportunity of studying numerous sections showing various alterations in these ~~glands~~ cells. It may be noted here that Renaut who originally (about 1879) regarded these islands as lymphoid, and described the pancreas as a lympho-glandular organ in his paper "on the lympho-glandular organs and the pancreas", has abandoned this view in his more recent "Treatise of Practical Histology" (1899) and regards these and the true acinar cells as having a common origin. Both the acini and these islands are richly provided with capillaries, but the network around the latter is much wider and comes into closer relation with the cells, having indeed a glomerular arrangement. This intimate relation of cells and capillaries suggests the furnishing of some important substance to the blood- something perhaps of the nature of an internal secretion.

The tubules leading from the acini open into the main pancreatic duct, or "Duct of Wirsung", running from left to right, and increasing in lumen in its progress. It approaches the posterior part of the head to finally unite with the common bile-duct in the duodenal wall at the ampulla of Vater. It was by the discovery of this duct in 1643 that Wirsung established the physiological action of the gland.

Santorini later described a second duct (called by his name) which lies in the upper part of the head of the organ, anastomoses at one extremity with Wirsung's duct and opens into the duodenum three quarters of an inch nearer the stomach than the larger duct. It narrows towards this opening. Claude Bernard, Henle, and Sappey described various abnormalities in these ducts, and in their openings into the duodenum which are of great importance, as numerous pathological changes have been found to be associated with these anatomical conditions. Opie who has done so much work on this gland, described a 100 cases, in more than half of which the two ducts were patent, and in which the duct of Wirsung was the larger. The duct of Santorini may occasionally act as a functionating outlet, but as a rule its secretion finds its way into the larger duct. In the remaining half of his cases the duct of Santorini was very narrow or occluded at its entrance into the duodenum. In general it may be said that the great bulk of secretion finds its way into the bowel by Wirsung's duct, and this opens with the common bile-duct (with which it pierces the duodenal wall obliquely) at a conical projection - the ampulla of Vater. Their course together is about 2 cm. Turning now to the secretion of the gland, we find that it is an alkaline colourless fluid, a quantitative analysis of which shows that it contains the following:-

Water----------97.6 per cent.

Organic solids---1.8 " "

Inorganic solids- 0.6 " "

The latter comprise chlorides of sodium and potassium and phosphates of calcium, magnesium and sodium, and it owes its alkalinity chiefly to this latter, along with traces of carbonates. The organic elements are much more important and embrace the following:- (1) trypsin, a proteolytic ferment of great power; (2) amylopsin, an amylolytic ferment; (3) steapsin, a fat-splitting ferment, and (4) a milk-curdling ferment. In addition to these ferments, there is a small amount of proteid matter, and traces of leucin, tyrosin, xanthin, and soaps.

Trypsin acts like pepsin, but in an alkaline medium, and more rapidly, and produces alkali-albumin instead of acid-albumin; its action is also carried further with production of such bodies as leucin and tyrosin. It is due to the loss of this ferment that the clinical manifestation of azotorrhoea is due; reference will be made to this later. Amylopsin is an active starch-inverter, possessing much greater power in this respect than ptyalin and being capable of acting even on unboiled starch; it is perhaps the most powerful of the pancreatic ferments.

The milk-curdling ferment is of entirely minor importance, milk being as a rule already curdled by the rennin and acid of the gastric juice before it enters the duodenum.

Steapsin or the fat ferment is of some special interest physiologically as being peculiar to the pancreas, and of great pathological significance as its action is the essential point in the phenomenon termed fat-necrosis. The normal action on fats is a two-fold one; in the first place it can emulsify them in virtue of its alkalinity, and its viscosity (due to the presence of proteid); and in the second place it possesses the important power of splitting fats chemically, producing glycerine and free fatty acids. The latter in their turn unite with alkaline bases to form soaps, which further aid the first mentioned process of emulsification. The following chemical equations will make the reaction clear:- taking stearin as a typical fat and potash as the alkali in the process of saponification we have the following interchange taking place:- (1). The ferment action splits the fat into glycerine and free fatty acid, through hydrolysis:-

$$C_3H_5\begin{cases} O.C_{17}H_{35}CO \\ O.C_{17}H_{35}CO \\ O.C_{17}H_{35}CO \end{cases} + 3\,H_2O = C_3H_5(OH)_3 + 3\,C_{17}H_{35}CO_2H$$

Stearin + water = glycerine + stearic acid

(2) The fatty acids now unites with a base to form a soap - saponification; thus:-

$$C_{17}H_{35}CO_2H + KOH = C_{17}H_{35}CO_2K + H_2O$$

Stearic acid = Pot. Stearate (Soap)

These soaps as well as the glycerine can now be absorbed. This chemical interchange resulting in the liberation of fatty acid and glycerine is of great

importance in disease of the gland, partly from the stand-point of fat-necrosis (an almost invariable accompaniment of grave pancreatic disease), and partly with regard to the so-called pancreatic reaction of Cammidge with which I shall deal fully in the course of this paper.

The painstaking work of Pawlow on the digestive glands demonstrated that the secretion of pancreatic juice was largely under nervous control, the main secretary nerve being the vagus, the sympathetic only acting in a subsidiary way. Pawlow describes very graphically (p. 58) the method of procedure adopted, in which the cervical vagus was divided, and four days later, after circulatory and other disturbances had ceased, was stimulated at its peripheral end by slow induction shocks. After a latent period of two minutes a steady flow of juice began from the permanent fistula he had made. Even after ceasing the stimulation, the flow continued spontaneously for several minutes longer. Other observers had suggested that the cause of the flow was due to the stimulation resulting from the acid gastric juice or contents flowing over the duodenal mucosa, and that of the jejunum, and further pointed out that it continued through the nerves to the pancreas and duodenum were cut. They regarded the action as a local reflex one, the centres of which were situated in the ganglia of the pancreas and in the solar plexus.

A new aspect however has been put upon this subject by the more recent researches of Bayliss and Starling and their isolation of the body named "Secretin" by them. They had already pointed out that a flow of juice could be obtained even though the nervous mechanism was eliminated, (including the ganglia - above mentioned). This led naturally to the idea of a direct action upon the gland by means of the blood-stream, but on injecting o.4 per cent hydrochloric acid into the blood-stream no flow was obtained indicating that it was not the acid itself of the gastric contents which was the essential factor. Further investigations showed that a special substance was produced in the intestinal mucosa, especially the duodenal, by the action of the acid, and that this body which they termed "Secretin" could produce an active flow of pancreatic juice when introduced into the blood-stream. This body, which is not a proteid but possibly some organic substance of no great molecular weight, is preceded in its formation by a mother-substance named "prosecretin", which alone has no power of stimulating the pancreas. Bainbridge in his paper on the "Adaptation of the Pancreas" affords further confirmation of Bayliss' and Starling's view (British Medical Journal), Vol. 1, page 778, 1904).

The Pathology of Affections of the Pancreas.

It is not my intention in this paper to enter into a full consideration of all the morbid conditions of the pancreas as these are so fully described in many excellent works both surgical and medical. It will be well however before proceeding to detail the clinical data on which diagnosis is founded, to give a short resume of the more important diseases to which this gland is liable.

1. Pancreatitis: acute and chronic. Like other viscera the pancreas may be the subject of inflammatory changes and these may be grouped under the two headings just enumerated. Acute pancreatitis in its simple form is a very rare disease, and arises usually from extension of gastro-intestinal inflammation along the pancreatic duct. It is an affection mainly of the male sex between the ages of 25 and 60, and there may be a preceding history of colicky attacks and indigestion. Although there may be a simple acute pancreatitis anatomically, it generally becomes a more complex condition, and accordingly Fitz describes under the acute inflammatory alteration three groups viz:- haemorrhagic, suppurative, and gangrenous, thus indicating their most striking features. (It may be noted here that haemorrhage may occur into the gland without inflammation). (a) Haemorrhagic pancreatitis. The immediate attack begins with very severe pain in the upper part of the abdomen, associated with vomiting and marked constipation.

Within a day or two symptoms of collapse will be manifest, and within a week a fatal issue usually supervenes. The autopsy reveals that the organ is enlarged, and engorged, and on incising it, its parenchymatous tissue is found to show necrosis, along with infiltration of blood into the interstitial tissue; some fibrinous exudate may exist. Bleeding also occurs in the neighbourhood of the pancreas, and fat-necrosis is found in the tubules of the gland and in the omentum and mesentery; antemortem clots have been found in the pancreatic vessels. The haemorrhage in this form is regarded usually as secondary, but it is clear that the difficulty of deciding whether it or the inflammation occur first is very great. It has been found possible experimentally to produce a very similar condition by injecting a variety of irritants such as solution of nitric acid, chloride of zinc, and so forth, and Hlava has formulated the view that the disease may be occasioned by gastric juice being driven into Wirsung's duct, by an anti-peristaltic action in the small bowel; but Opie considers that this theory has not been substantiated, and regards the fat-necrosis as an essential point in the pathogenesis, and thus it may possibly happen that the bleeding may occur before any true inflammatory change has taken place. It must be kept in mind as a possible factor, that pancreatic juice can attack the gland itself, if it infiltrates it, provided

always that it has been previously damaged. Lastly it may be mentioned that various observers have found acute pancreatitis with bleeding, associated with the presence of a gall-stone impacted near the orifice of the common duct, or impacted in the very orifice of the diverticulum of Vater. In the latter case the orifice is occluded but neither the common bile-duct nor the pancreatic duct, and the pressure in the former being often the greater bile may be forced into the duct of Wirsung staining it green. To ascertain if the bile could have any harmful effect on pancreatic tissue, experiments were performed at the John Hopkin's Hospital under Opie's directions, and described in the Bulletin of the Hospital for 1901, and it was found as an actual fact, that bile finding its way into the gland could cause haemorrhagic pancreatitis with scattered foci of fat-necrosis. This is an interesting point, but such a phenomenon probably only accounts for a certain number (probably few) of the cases, and can only occur, as Opie himself points out, in 3o per cent of individuals, on account of the anatomical arrangement of the ducts and the ampulla.

(b). Suppurative Pancreatitis. This resembles suppuration in other organs. Foci of pus occur throughout the gland, and large abscess cavities are of common occurrence. The condition may last weeks or months, and usually ends either by extension to the liver (with pylephlebitis and hepatic abscess),

or the abscess cavity bursting into the stomach or duodenum, discharges its contents. Further the lesser peritoneal sac may become the receptacle for the contents of the ruptured abscess cavity, and grow to a considerable size forming a well-marked tumour in the epigastric region. Fitz points out that fat-necrosis is uncommon in this affection of the organ, though always present in the haemorrhagic or gangrenous variety. Suppuration in the gland is rather a secondary change and does not bear the same intimate relation to the haemorrhagic form of pancreatitis as does the gangrenous variety.

(c). Gangrenous Pancreatitis. This is usually preceded by the acute haemorrhagic condition and may last several weeks. The necrotic parenchyma becomes invaded by bacteria, and death of tissue ensues, the gland being changed into a large black softened mass; the surrounding tissues share in this loss of vitality. The lesser peritoneal sac becomes infected, peritonitis is set up, and it (the sac) is converted into a large abscess cavity containing pus, blood, and necrosed tissue. Disseminated foci of fat-necrosis are well marked. It may be said that gangrenous pancreatitis is but a final stage in the acute haemorrhagic variety provided the fatal issue be sufficiently long postponed.

11. Haemorrhage into the Pancreas apart from Inflammation (Pancreatic Apoplexy).

Apart from the haemorrhagic pancreatitis first

described, a very interesting condition has been put on record by Speirs, Zenker, and other writers, as occurring in the gland viz:- bleeding into the organ, without evidence of inflammation either from a clinical or pathological aspect. From its analogy to haemorrhage from the cerebral vessels, this ~~organ~~ condition has been termed "pancreatic apoplexy". Haemorrhage from traumatism, acute infectious diseases, blood-dyscrasias, and other causes, does occur in the pancreas as in other organs, but is here, except in case of direct injury, the evidence of the effect of a widely distributed or general cause. In a case of Seitz's no disease was found, excepting the haemorrhagic condition of the gland, to explain a sudden and fatal issue. Klebs considered the bleeding to be due to the corroding action of the pancreatic ~~piece~~ juice on the blood-vessels, and Fitz found, that, on injecting fluids into the blood-vessels post-mortem, some of it escaped from the vessels. He further points out that in arterio-sclerosis owing to the liability on the part of the vessels to rupture, the haemorrhage may follow, but adds that arterial degeneration is uncommon in these conditions. Seitz corroborates Fitz's idea of arterio-sclerosis being a possible factor, and mentions cases in which the two have co-existed. It seems to me however difficult to assume arterio-sclerosis as the main factor for there is little doubt if one accepts this view, that

haemorrhage into the gland would be a much more common occurrence than it is. The liability to rupture of the pancreatic vessels would appear to be a minor factor in etiology, considering the extensive vascular supply of the organ, and the frequent incidence of arterio-sclerosis. The fact that Seitz has described cases in which haemorrhage and arterio sclerosis co-existed is no evidence in favour of the latter being the main causative lesion. Some perverted state of the pancreatic secretion, whereby as Klebs suggests it acquires a corrosive action may possibly explain the condition. Fat-necrosus is not so marked in those cases as to give a reason for the haemorrhage.

From the foregoing we may conclude that pancreatic apoplexy and haemorrhagic and gangrenous pancreatitis are related to one another, though Seitz on reviewing the literature in unable to find any reason for supposing inflammation to precede pancreatic apoplexy so-called.

3. Chronic Interstitial Pancreatitis.

This is generally a slow and chronic process ab initio being associated ~~with~~ rather with changes in other organs than with a preceding acute stage in the gland. Thus it may occur in the course of chronic valvular disease, in portal obstruction or in emphysema, a gradual induration being induced through passive congestion. The symptoms are quite subordinate to those of the primary lesion.

It certainly does happen occasionally that a chronic fibrosis may supervene on a suppurative pancreatitis, but the condition here is after all suppurative throughout. There is however a genuine chronic pancreatitis not associated with heart or liver disease but apparently occurring ~~perse~~ per se and of great interest in modern pathology on account of its proved association with disturbances in the metabolism of sugar. Further there is a well-defined form of chronic pancreatitis related to congenital syphilis and described first by Birsch-Hirschfeld, and later by Schlesinger. In this variety the islands of Langerhans are not implicated, but there is a chronic interstitial change between the tubules showing numerous epithelial and lymphoid cells, and the acini suffer atrophy. Amongst the chronic interstitial tissue little groups of cells persist unaltered and these are the islands of Langerhans. There is some difference of opinion as to whether these changes occur in the foetus in utero or whether they only show themselves after the full-time child is born. Besides these forms of pancreatitis mentioned, chronic changes in the gland appear to be frequently associated with alcoholism, and to some extent also with tuberculosis, ulcers and tumours of the stomach, aneurysm of the aorta or caeliac axis or disease of the spine.

Anatomically, the inflammatory change may be essentially inter-lobular or inter-acinar. In the

former the lobules are separated by well marked interstitial fibrosis and the acini in places are atrophied and disappear. The islands of Langerhans escape, and this may be attributed to their better vascular supply, their separateness from the ducts by which they escape the action of irritants and their situation in the centre of the lobules which are generally attacked at the periphery. In the inter-acinar variety on the other hand the fibrous tissue penetrates the lobules and is in excess of any lobular change. The glandular tissue is completely changed being replaced by much atrophied acini. The islands of Langerhans become incapsulated by this invading fibrous tissue, which may penetrate within the islands themselves, separating and compressing the cells. The latter themselves become altered and their nuclei stain more deeply than usual. It is a change of this kind that is associated with alterations in the metabolism of carbohydrates. It may be mentioned in connection with the pathology of these chronic changes that they may be found associated with hepatic cirrhosis. Both probably owe their origin to a common cause. In those cases of chronic pancreatitis associated with diabetes hyaline degeneration of the islands of Langerhans has also been noted - Opie, /page 215/ describes a very remarkable instance of this in a young diabetic woman where not only the islands of Langerhans but the parenchyma generally was the seat

of hyaline change, the hyaline matter being deposited between the cells and the capillaries. In conclusion the symptoms of chronic inflammation of the pancreas are somewhat vague. They embrace gastro-~~interstitial~~ intestinal disturbances, emaciation, loss of strength and tenderness on pressure. The spleen may be enlarged. Such objective phenomena as glycosuria, fatty stools and so forth, will be considered in the next section dealing with the clinical data on which diagnosis of affections of this gland rests.

4. Pancreatic calculi. The presence of stones in the pancreas is usually accounted for by a preceding inflammation of the duct wall leading to difficulty in outflow of the secretion, or by some condition outside the duct leading to the same result. The retained secretion undergoes changes leading to a precipitation of certain of its salts - chiefly carbonate and phosphate of lime along with some cholesterin. As in gall-stones their number may vary from one to many and in size from small grains to masses as large as a hazel-nut or even bigger. They do not appear often to be facetted, and are lighter in tint than gall-stones being grey or white, and not infrequently spinous or dendritic like coral. They have been known to ulcerate through leading to the formation of fistulae between the pancreas on the one hand, and the stomach, duodenum, or peritoneal cavity on the other. Carcinoma of the gland has been described as occurring along with calculus, but in my opinion

this may happen to be merely a coincidence and I do not think there is the same ~~casual~~ causal connection between the two as there is between gall-stones and malignant disease of the liver.

Symptoms may be absent, or there may be paroxysmal attacks of pain, analogous to that of biliary colic, radiating along the left costal margin to the spine and shoulder-blade. Jaundice may be noted. In some instances there are merely the indeterminate symptoms of a fibrous pancreatitis.

5. Cysts of the pancreas. The occurrence of these is a rare morbid affection of the gland. In Guy's Hospital out of 6000 autopsies only three instances of pancreatic cyst occurred. It is equally common in the two sexes, and is met with generally in adult life but may occur at any age. Richardson for example described a case of cyst of the pancreas in an infant of 14 months and this points to the possibility of a congenital origin.

When we turn to etiology we find according to Fitz, that cysts may follow extension of inflammation from duodenum along the ducts causing obstruction and retention of the secretion, pressure of tumours and the existence of calculi bringing about the same result. Durante has described a pancreatic cyst due to obstruction by a lumbricoid worm. Formerly traumatism was considered an important and direct cause; now the view is rather maintained that the injury may set up a localized pancreatitis and that cyst-

formation may be secondary to this, the cysts occurring not only in the gland but in the lesser peritoneal sac. Another mode of origin may be the development of a cystoma or cystic tumour in the pancreas, very analogous to that occurring in the ovary. Finally cysts may occur in the pancreas in general cystic disease.

In looking at the morbid anatomy, we find that the cysts vary much in size and in number, they may be quite small or may even attain the size of the pregnant uterus at term. The duct of Wirsung may be completely occluded or may be present in the cyst cavity. They are smooth on the surface or somewhat nodulated, are lined by cylindrical epithelium and may open into one another. They lie behind the lesser peritoneal sac and may even adhere to the peritoneum. The lateral pressure they exert may lead to atrophy of the gland-parenchyma, which in a damaged form, may be found lying between the cysts. A large syst may contain 3 gallons or more (14 - 15 litres) of a greyish white colour, viscid or watery in consistency, and alkaline in reaction. The specific gravity varies from 1010 to 1020 and the tint may be altered from the presence of blood. The microscope shows epithelial debris; leucocytes, fat-cells, cholesterin, leucin and tyrosin. Acicular crystals (? fatty) have also been found. The fluid from such cysts may possess all the qualities of pancreatic juice in that it can emalsify fat, invert

starch and peptonize proteids.

The symptoms of pancreatic cyst remain in abeyance till it has attained a size sufficient to produce some mechanical effect. It is slow in growth and may remain quiescent for a long period; or it may attain a great size in a few months after an attack of pain and vomiting. In diagnosis the limits of such a cyst may be mapped out by ~~finding~~ inflating both colon and stomach (the former with water and the latter with gas) and keeping the hips raised. Haemorrhage may occur into a cyst. It is clear that much valuable information may be got by the chemical examination of fluid from a tapped cyst. Very rarely an echinococcus cyst may occur.

6. Neoplasms of the pancreas. The varieties of these are few. Among the benign we find tubercular masses, adenoma and the cystoma already mentioned. The ~~maig~~ malignant comprise sarcoma and carcinoma, the latter being encephaloid or scirrhus. The incidence of the latter affection (cancer) is estimated at about 6% of all cancers. Mayo Robson quotes that out of 53,000 necropsies gathered from various sources where the examinations were presumably carefully made, there were 226 cases of primary malignant disease of the pancreas, but as these include Remo Segre's cases from the Ospadale Maggiore (Milan) in which the primary and secondary growths were not separated, the proportion of primary growths is not so large. Cancer of the gland generally occurs after the age

of 40, and more than 60% of the patients are males. It may however occur in childhood, in infants, and has even been found at birth. Any part of the gland may be affected but the head is the most common site. It may be circumscribed or may infiltrate the whole organ. By its growth it forms adhesions to adjacent organs, and may by pressure on the pylorus cause dilatation of the stomach, or by pressure on the common bile-duct lead to great enlargement of the gall-bladder. The adjacent lymphatic glands become the seat of metastasis and secondary nodules may be found in the liver and spleen. In chronic interstitial pancreatitis Mayo Robson has described enlargement of the glands in the lesser omentum, but here they are discrete; in cancer they are confluent. Chronic inflammation may even from its hardness be mistaken for cancer in the head of the organ. Although as already mentioned, encephaloid and scirrhus cancer are the most common varieties, columnar-celled epithelioma and colloid cancer have been found. Sarcoma of the pancreas may be described in a word:- it is a very rare and clinically is practically indistinguishable from cancer.
As regards symptomatology, digestive disturbances usually usher in the morbid phenomena. Jaundice appears in practically all cases, increases gradually and becomes both extreme and persistent. The gall-bladder is distended and palpable, and the liver may show enlargement as a whole. A tumour may be

discovered in the region of the pancreas and emaciation and cachexia usually rapidly follow, the patient becoming greatly prostrated. After the onset of Jaundice the disease generally runs a course of from six to eight months. The stools are bulky and may contain undigested fat and muscle fibre, and free fatty acids. The urine may be albuminous but does not generally contain either sugar or fat. With increasing growth of the neoplasm the pressure symptoms become more marked and vary according to the position of the tumour and direction of growth; thus we may find ascites, oedema of the lower extremities, engorgement of the superficial veins and so on.
This concludes the summary of the affections of the pancreas.

<u>A consideration of certain clinical data on which Diagnosis of Pancreatic Disease is based.</u>

In this section I propose to consider shortly the more important clinical manipulations on which reliance is placed in making a diagnosis of ~~the pancreas~~ disease of the pancreas. The symptoms as I have already remarked, are, as far as the patient's feelings go, of a very general and indeterminate character, and physician and surgeon alike are ready to grasp any clear and reliable sign which may aid them. I do not purpose discussing the general physical examination of the abdomen, but shall confine myself to a special group of indicative signs, based chiefly on alteration in the function of the gland.

1. GLYCOSURIA.

Moynihan (in his recent paper on "The value and significance of certain signs and symptoms of Pancreatic Disease"), (British Medical Journal, Vol.11 page 1740, 1904) calls to our remembrance the fact that as far back as 1788, Cowley described a case of Glycosuria associated with disease of the pancreas. This was confirmed later by Bright. The matter however did not assume any great importance or awaken any special interest till the classical experiments of Von Mering and Minkowski (1886) on dogs fully demonstrated the relationship between pancreatic extirpation and diabetes. They removal of the whole gland they found, led to the establishment of a true diabetes, which was not the case if the ablation was only partial. Further investigating the assimilation of sugar, they noted that in a dog with the pancreas partially removed, glycosuria although not present on an ordinary diet could be produced by increasing the amount of sugar in the diet; to this phenomenon the term " alimentary glycosuria" which is still employed was given. The question next arose as to whether this condition was due to the loss of the ordinary secretion of the gland, and Schäfer and Laguesse determined that this was not the case since ligation of the pancreatic duct did not lead to the appearance of sugar in the urine, nor did injury to the nervous supply of the gland. Further if a portion of gland was transplanted into the subcutaneous tissue (the rest being removed) no glycosuria ensued as long as the vascular supply of the transplanted part was intact.

If the nerves of the transplanted part were divided, no sugar appeared, but if the part itself were taken away, glycosuria followed. This at once led to the suggestion of an internal secretion of the pancreas and Lepine and later Sumacek have isolated a ~~glycosur~~ glycolytic ferment from a pancreas which they considered to be an active agent in assimilation of sugar; and the frequent if not constant presence of histological changes in the islands of Langerhans in cases of pancreatic diabetes led to the natural conclusion that these were in some way responsible for this so-called secretion. Investigations into this have been conducted chiefly by Ssobolew and Opie, and changes of a hyaline character have been observed in the islands, and in general the evidence points strongly to the effect which these cells exercise on carbohydrate metabolism. Hansemann has pointed out that atrophy of the pancreas with interstitial change is the most common lesion found in the pancreas in those cases of diabetes due to disease of that organ. It is not sufficient for the prevention of glycosuria in dogs to have only a very small portion of the gland; a reasonable proportion of its substance must remain.

It must however be kept in mind that so far pancreatic lesions of a distinct character have been found in only some 50% of fatal diabetic cases; the remainder as well as minor instances of glycosuria may possibly result from totally different antecedent causes. Among these latter we may include certain diseases of the

nervous system such as cerebral tumour. Acromegaly and perhaps also exophthalmic goitre; under this heading one may include experimentally-induced glycosuria, arising from removal of the superior cervical sympathetic ganglion, puncture of the floor of the fourth ventricle just in front of the calamus Scriptorius, section~~a~~ and ~~an~~ stimulation of the spinal cord at the level of the brachial flexus, and stimulation of other divided nerves. In the next place hepatic derangement, both functional and organic, may lead to the appearance of sugar in the urine. It has been found in cirrhosis of that organ, and frequently in temporary disorder of its function. Opie (p. 272 has found however chronic pancreatitis associated with hepatic cirrhosis). Again, various chemical agents, among which phloridzin takes the chief place, are capable of causing grape-sugar to be present in the urine, but not only does this occur when the substance is swallowed, but even when it is respired as in the case of carbonic monoxide gas. In the latter instance the glycosuria disappears when the chemical agent ceases to be ingested. What reliance then, is to be placed as far as glycosuria is concerned, in making a diagnosis of disease of the pancreas? The answer that must be given to this in our present state of knowledge is, that, taken alone, ~~does~~ glycosuria does not warrant one in making a diagnosis of disease of the pancreas. It does become of importance when taken in conjunction with other phenomena and in every case a careful examination for

sugar, even in small quantities should be made, for it is possible that an alimentary glycosuria may be an early warning sign of the onset of pancreatic mischief. It is also of importance to ascertain the minimum amount of grape-sugar ingested that will lead to any glycosuria whatever. A healthy person should be able to assimulate up to about 150 grms.

2. HAEMOCHROMATOSIS.

This consists in a deposit of pigment granules in most of the glandular organs of the body, chiefly in the secreting cells which take on a reddish-brown colour. The pigment contains iron and has been called by Recklinghausen "haemosiderin". Besides this there is also a deposit of smaller granules in the muscle-fibres of stomach and intestines, in the walls of lymph and blood-vessels and in connective tissue. The latter being iron free is called "haemofuscin". The skin is of course affected as well as the internal structures. In cases of Von Recklinghausen with cirrhosis of the liver there was widespread pigmentation, and later the French writers described cases of diabetes with bronzing of the skin, and widespread pigmentation in organs. The pigment being of the nature of haemosiderin. To this condition they gave the title of "Diabete Bronzée". Most authorities believe that the bronzing in this condition is secondary to the diabetes, and not a primary condition. In some cases haemorrhages have been found, e.g. into pleura, peritoneum, and meninges and from this it has been concluded that the pigment

is due to the breaking up of this extravasated blood. In many cases however no such causal condition has been found. On the other hand in diabetes in general no such bronzing occurs, nor any excessive deposit of iron on the liver. In all cases of bronzing that have been carefully examined histologically lesions of the pancreas, of the nature of a chronic interstitial change, have been found as well as similar alterations in the liver. It must however be kept in mind that in many cases of chronic pancreatitis and cirrhosis of the liver no such discolouration of the skin occurs. Opie (p. 201) puts forward the view that the chronic changes seen in the pancreas are due first to pigmentary degeneration of the parenchymatous cells, and secondly to irritation produced by the presence of the pigment in the interstitial tissue. The change is of the interacinar type and affects the islands of Langerhans. In simple haemochromatosis without diabetes it is supposed that the changes have not proceeded far enough to destroy a sufficient number of the Langerhans' cells. From the fore-going it will be seen that while the presence of haemochromatosis is a valuable indication of chronic pancreatic mischief, its absence does not warrant one in stating that no pancreatic disease exists. It is therefore of modified use as a diagnostic factor.

3. Azotorrhoea.

Fles was the first to describe the presence of undigested proteid material in the stools, and to this phenomenon he gave the name of azotorrhoea, or a flowing away of nitrogen. In a case he described, he found chronic pancreatitis (post-mortem) and during life there was a large amount of undigested nitrogenous material passed by the bowel. In cases of diabetes, Hirschfield found that sometimes as much as 30 per cent of the proteid taken was passed in the stools, and experimentally it has been shown that after ablation of the pancreas in the dog 54 per cent of the proteid escaped digestion while in partial ablation only about 40 per cent escaped. The natural explanation of this is the loss of the pancreatic secretion with its active proteolytic ferment trypsin but Abelmann suggests that another cause lies in the associated presence of undigested fat which interferes with proteid assimilation or digestion. It may be asked however whether azotorrhoea is not met with under other conditions. The answer to this is in the affirmative. It has been found in diarrhoea, of a persistent kind, and in cases where there has been the ingestion of a large amount of meat. As regards its detection clinically, the microscope is of course of great aid, but for real accuracy some chemical method such as Kjeldahl's, for the precise estimation of nitrogen, should be employed. When we ask ourselves what is

the ultimate diagnostic value of this condition we must keep in mind the dictum of Fitz which I give verbatim: "Any significant increase of undigested muscle-fibres in the stools would be expected only when there was extreme diminution of pancreatic juice in the bowel, gastric digestion was relatively normal, the diet contained no excess of meat and there was no diarrhoea". Another method of testing for the presence and efficiency of the pancreatic ferment is to give some special body on which it is known to act. Sahli for example suggested that iodoform should be given in glutoid capsules treated with formalin, so as to eliminate the gastric digestion. If the individual be normal the pancreatic secretion attacks the capsules and in the case of iodoform, the iodine reaction can be got from the saliva, as soon as the intestinal digestion begins; in the case of salol salicylic acid appears in the urine. This has been designated the "signe de Sahli". Sahli found in a series of cases where the reaction was much delayed, i.e. to 24 hours that there was cancer of the head of the pancreas. This procedure, simple and clear as it may seem is not withour possibility of error. In the first place we must suppose that the stomach possesses normal motor power, so as to pass on the capsule to the duodenum in a reasonable time; in the second place, there is a normal gastric secretion so as to stimulate the pancreatic flow. Further there must be a normal

absorptive power on the part of the intestine. And after all even though there be disease of the pancreas, perhaps well-marked, there may be still sufficient pancreatic secretion entering the duodenum to cause a positive result; this was noted in a case of cancer of the head of the gland recorded last year by Sir T. Lauder Brunton. So that conclusions of any real use can only be drawn when with an apparently normal gastric digestion and intestinal absorption, entirely negative results are obtained, and the difficulty of recognizing the necessary normal condition on the part of the stomach and bowel render the test of little diagnostic value. And as regards azotorrhoea chiefly, it is only of importance when taken in conjunction with other data, of which steatorrhoea is one of the most important.

4. Steatorrhoea.

This term signifies the passage of fat in the stools, and for many years was regarded as an almost certain sign of disease of the pancreas, especially where jaundice was absent. It was described 85 years ago by Kuntzmann and has been much studied since that time. His case was one of chronic induration of the gland, and abundance of fat was found in the stools. Other observers noticed the same phenomenon but in so much as jaundice was often present in association with disease of the pancreas it was difficult to say whether the undigested fat was not due to the absence of bile. Muller, the great physiologist, attributed the fatty stools entirely to the want of

bile. Claude Bernard however destroyed the pancreas in dogs by injecting oil into the main duct, and found thereafter that the greater part of the fat given by the mouth (if unemulsified) was passed undigested. This was further substantiated by Abelmann's observations after complete removal of the pancreas in a dog.

The best account I have seen of steatorrhoea, in relation to disease of the pancreas in man, is found in R.H. Fitz's paper on Symptomatology and Diagnosis of Disease of the Pancreas published in the Transactions of the Congress of American Physicians and Surgeons, held at Boston in 1903 p. 39. He considers it to be one of the chief data on which diagnosis may be based provided certain elements of fallacy can be excluded. In this condition the stools assume a solid or liquid form, their colour is white or grey, they are not infrequently bulky, and even by the naked eye the presence of oil or fat may be detected. The concomitant occurrence of jaundice is important, some authorities considering that this is a leading cause of fallacy, while Muller thinks that the absence of bile is necessary for steatorrhoea, as well as that of the pancreatic juice. He considers that the latter influences chiefly the split fats. Fitz himself however does not consider that the presence of jaundice is an important factor, in the production of fatty stools connected with disease of the pancreas, and gives a table of cases in support of this. In this table

in which cancer and calculus were the chief morbid conditions, he shows that in some three-fifths of the cases of steatorrhoea attributable to pancreatic diseases there is neither diabetes nor jaundice, while in two-fifths there is either diabetes or jaundice, in about equal proportion; in but few instances was there a combination of both. In a diabetic case of Fles where atrophy of the pancreas was found post-mortem, and in which during life large quantities of undigested fat, and muscle-fibre were passed, the administration of the extract of a fresh pancreas daily led to the disappearance of all the fat and of much of the undigested proteid. Where the extract was left off, these substances reappeared in the faeces. During the treatment the amount of urine and glucose excreted underwent no change.

The mere presence of fat in the stools however, does not warrant a diagnosis of disease of the pancreas, since as much as 5 to 10 per cent of the fat ingested by a healthy person may pass away in the stools. Further in jaundice, even of the catarrhal tye, this amount is doubled, and in disease of the mesenteric glands and intestines the amount excreted is also increased. From what has been said it will be clear that the mere presence of fat in the stools is of no real importance, while if an excess be taken a good deal may appear. Secondly the occurrence of a considerable degree of steatorrhoea

in cases where there is jaundice is held by most observers to be a doubtful sign of pancreatic disease, and Muller as already noted, agrees with this. Thirdly when steatorrhoea and azotorrhoea occur without jaundice it is ~~strongly~~ a strong presumptive sign of a pancreatic lesion. Lastly if one finds steatorrhoea, azotorrhoea, diabetes and an epigastric tumour, the diagnosis is assured.

5. Jaundice.

The consideration of this need not detain us long. It depends mainly on the anatomical relationship of of the pancreatic and bile-ducts, and is most common in cases of chronic pancreatitis affecting the duct, and in cancer of the head of the gland. A slight icteric tinge has also been noted in acute pancreatitis, generally due to an impacted stone in the ampulla of V ater. In cancer especially the jaundice is well-marked, begins insidiously, increases steadily, and at last becomes profound and is permanent. Along with this there is usually a tumour caused by distension of the gall-bladder and enlargement of the liver, the occurrence of these three ~~sings~~ signs together is termed "Courevisier's law.

6. Fat-necrosis.

This is not a clinical datum except where surgical interference has taken place, and the abdomen has been opened. As it stands therefore, it itself cannot directly be a means of diagnosis with a view, let us say, to operation. The outcome of this is that

clinicians now seek for indirect evidence of its existence, as for example in Cammidge's so-called pancreatic reaction.

Fat-necrosis was first definitely described by Basler in 1882. He noted in doing autopsies that minute white opaque areas could be seen around the pancreas and in two cases larger areas in the fat of the omentum, peritoneum and retro-peritoneal tissues. To the latter well-marked state the name of Multiple or Disseminated fat-necrosis was given. These areas were shown to be composed of fat-cells, and subsequent observers established the connection between this condition and pancreatic disease. The minute foci on the other hand (which were first mentioned) are often found at post-mortem and have definitely been shown to be due to self digestion of the pancreas occurring shortly before or at the time of death. I shall refer to this again.

Round the genuine areas of fat-necrosis haemorrhagic zones may be generally seen; the areas are limited usually to the abdomen, although more widespread necrosis affecting the subpleural and subpericardial fat has occasionally been noted. As regards etiology, Fitz first suggested that it was due to a lesion of the pancreas, generally a haemorrhagic or gangrenous pancreatitis, more rarely a suppurative or chronic interstitial inflammation. Langerhans was the first to work out the histological and chemical nature of fat-necrosis. He found the necrosis was dependent

on a splitting of the fat into its component parts- fatty acids and glycerine. The former are deposited in the necrotic cells as needles, and the glycerine is absorbed. After sometime the fatty acids combine with calcium salts, which are deposited in the cells as globular masses; a proliferation occurs in the tissue cells around the necrotic areas, chiefly in the connective tissue, and to some extent demarcates the necrotic areas. In these areas large cells, like giant cells may be seen, being fat cells undergoing proliferation. As reggrds the precise method of causation, it was suggested that bacterial invasion might cause it, among the organisms suggested being the colon-bacillus. The findings however were inconstant and observers began to seek another cause. The histologico-chemical work of Langerhans and the isolation of a fat-splitting ferment in the necrotic areas by Flexner lent strong support to the view that someting definitely connected with the pancreas itself was at issue. Numerous experiments to determine this were carried out by Langerhans, Hildebrand, and Dettmir, and consisted in ligaturing of the ~~entrance-of-the-secretion~~ organ, division of the organ, and the allowing of the entrance of the secretion into the general peritoneal cavity. From these experiments it was concluded (Hildebrand) that obstruction to the outflow of secretion alone or combined with obstruction to venous return, or the escape of pancreatic juice into the general peritoneal cavity resulted in typical fat-necrosis about the pancreas,

and in the omentum and mesentery. Numerous other observers have confirmed these views. Katz and Winkler in their experiments tied many ligatures round the gland and in this way produced well-marked fat-necrosis with haemorrhagic pancreatitis. From the fore-going they conclude that the fat-splitting ferment is the main factor in the production of fat-necrosis and that its activity is increased by arrested blood supply and infiltration of the organ with blood causing a lowered resistance of the part. In all these experiments however, in no case was the fat-necrosis so widely disseminated as in the human subject.

Mere escape however of pancreatic secretion would not account as Opie points out for those ~~early~~ cases of widely distributed fat-necrosis where for example, the sub-pleural fat is affected. He was able, by ligaturing the pancreatic ducts in the cat to produce widespread necrosis, provided the animal lived long enough. It was necessary to have a thorough infiltration of the surrounding tissues with the secretion. In some instances detaching the gastro-hepatic omentum, he drew its right border through between the pancreas and duodenum, the head of the pancreas having previously been separated from its duodenal attachment. It is to be noted that in these experiments, the vascular supply remained practically untouched and therefore Opie concluded that ligature of the duct alone was sufficient to produce the necrotic lesion, the fat-splitting ferment gradually diffus-

diffusing itself. In one case he found no dissemination though the animal lived 25 days; post-mortem the gland was found to be in a state of advanced chronic interstitial inflammation; he thinks this limited the diffusion of the secretion.

As a phenomenon in the course of pancreatic disease, fat-necrosis occurs most commonly in conditions where the duct is obstructed by a calculus, by the presence of malignant disease in the head of the gland, or by the contraction of fibrous tissue occluding the lumen of the smaller ducts. If there be great fibrous induration with atrophy of the gland, the fat-necrosis is limited. The condition is also found in acute inflammation of the pancreas, and to a less extent in chronic cases, where the induration is not very far advanced,- and where a calculus is present.

Self-Digestion of the Pancreas.

Minute areas of necrosis which have been already described are often found at autopsies, and have definitely been proved to be due to self-digestion of the pancreas; and from a study of 75 cases by Chiari, about 50 per cent showed this change. From its occurrence only a few hours after death it has no relation to putrefactive changes. The whole organ may be involved, both interstitial and parenchymatous tissue being affected. The name para-pancreatic necrosis has been applied to this condition. Self-digestion of the pancreas without fat-necrosis may occur and this shows that post-mortem contact of the tissues with the pancreatic juice is sufficient. Chiari considered it to be an agonal or ante-mortem change, as the association of haemorrhage with it

(into the organ) could only be accounted for in this supposition. He thought the disintegrating effect of the bleeding allowed the secretion to escape, while the associated lowered vitality allowed of its action on the tissues during life. In a few cases of para-pancreatic necrosis real disease of the organ has been found generally of the nature of a chronic interstitial change with duct obstruction. In other cases stagnation of the pancreatic secretion before death (whereby it becomes diffused into the tissues) has been suggested (by Opie) as the cause of the phenomenon; since in cases examined by him the duct was found filled with very viscid secretion. This theory however seems to me far-fetched and inadequate as little pancreatic juice can be secreted in most cases at least for hours before death. This might occur possibly where a calculus was lodged in the duct and displaced in the last struggles. (Opie p.162) believes that it may arise from various causes of which agonal ante-mortem ~~dig~~ self-digestion has a place.

Section 1V. A special consideration of the so-called "Pancreatic Reaction".

The clinical phenomena already described when taken in conjunction one with another enable the clinician to make a diagnosis of pancreatic disease. The invariable appearance of many of those data however, even where well-marked pancreatic disease is established, allows of no specific factor being associated with disease of that organ. Lately a new

aspect has been put upon the subject, by the description by P.J. Cammidge of a specific urinary reaction based on the assumption that a definite substance is excreted in the urine in cases of this disease. He assumes fat-necrosis to occur in all forms of inflammation of the gland especially acute and gangrenous pancreatitis, and even in cancer of the organ. In this fat-necrosis the neutral fat is split into its radicles,- fatty acid and glycerine (see p.); the former unites with lime-salts and remains in situ, while the glycerine is absorbed into the blood. Being unable to detect the glycerine in the blood on account of the small amount of the latter available, clinically, he turned to the urine as a likely material in which to discover it. He believed it could be found there, as Catillon had demonstrated its presence after administration of glycerine by mouth to animals, recovering as much as 50 per cent of that ingested. Dr. Cammidge next pointed out that one would look for even a larger ~~propertion~~ percentage of glycerine in cases of pancreatic disease owing to the deficient oxidation, which, as he says, "apparently" accompanies any glandular mischief. Numerous methods had been already devised for the detection of glycerine in urine. That most commonly employed was to extract the glycerine with absolute alcohol after evaporation to small bulk, driving off the alcohol and finally extracting the glycerine from the residue by a mixture of equal volumes of alcohol and ether. When the menstrua were

driven off by gentle heat the glycerine remained behind. This method I have employed on a number of instances. The glycerine may be detected by the following tests:-

(1). A little may be heated with a crystal or two of potassium hydrogen sulphate ($KHSO_4$) in a test tube, when the irritating odour of acrolein is perceived: the latter is produced by the dehydration of glycerine thus; $C_3H_5(OH)_3 - 2H_2O = CH_2CHCOH$ (glycerin) acrolein or acrylic aldehyde.

(2). It brings back the colour of carbol-fuchsin previously decolourised by sulphuric acid.

(3). It turns Nessler's reagent brown;

(4). And when burned with borax, it gives a green flame. (From Catillon and Salkowski). Another method for detecting glycerine in urine is based on the fact that oxalic acid in the presence of glycerine breaks up into formic and carbonic acids. This method had been employed by Lewin. Neither of these procedures appeared to Dr. Cammidge satisfactory for the detection of minute quantities of glycerine, so he elaborated a new method based on the hypothesis that on boiling the glycerine-containing urine with nitric acid glycerin would be produced, from which in its turn, by using Phenyl Hydrazin an osazone could be obtained. In carrying out the method he was struck by the well-formed crystals obtained in pancreatic cases and the entirely negative results given by normal urines, and those from other diseases

such as catarrhal and obstructive jaundice, intestinal obstruction, gastric ulcer etc. He afterwards found that crystals were also obtained from urine of patients in whom rapid tissue change was going on, with deficient oxidation. He was of course aware that the reducing power of all urines is increased on boiling with mineral acids, due probably to the presence of animal gum but he was unable to correlate the presence of this body with his reaction in pancreatic cases.

From fallacy due to the great oxidising power of nitric acid, this simple method had to be abandoned and another evolved, which is the basis of the so-called pancreatic reaction in urine, which as already mentioned forms the chief part of his Arris and Gale Lectures for 1904. The method deals with two separate reactions termed "A" and "B" and the procedure is as follows. The urine must first be examined to exclude albumen and sugar, as even minute traces of the latter would cause a fallacy, the phenyl-hydrazin test should also be apllied. If sugar exist it must be removed by full fermentation. Albumen also must be removed if present.

In Reaction "A" 10 ccm of the carefully filtered urine are placed in a small glass flask, and to this 1 ccm. of strong hydrochloric acid is added. The mixture is then gently boiled on a sand bath for 10 minutes after the first sign of ebullition, a small filter being placed in the mouth of the flask to act as a condenser. To the flask are now added

5 ccm. of the filtered urine, and 5 ccm. of distilled water, and the whole rapidly cooled in running water. The mixture is now strongly acid, and the excess of free acid is neutralized by slowly adding 4 grms. of lead carbonate, and allowing 3 or 4 minutes for the completion of the reaction. The neutralized mixture is now filtered through moistened filter-paper and the flask washed out with 5 ccm. of distilled water on to the filter. To the clear filtrate are then added 2 grms. of sodium acetate and 0.75 grms. of hydrochloride of phenyl-hydrazin, and the whole is boiled for 3 or 4 minutes on a sand bath. The hot fluid is now poured into a test-tube and allowed to cool, after 1 - 24 hours according to the gravity of the case a flocculent yellow deposit is found to have settled down, and when examined by a 1/6th. inch objective reveals, in a positive case, crystals in sheaves or rosettes of a golden yellow colour. It was found that Reaction "A" might give a positive result in other cases than those of disease of the pancreas, such as pneumonia, cancer, adenitis etc. and accordingly another procedure was evolved (to obviate these fallacies), which in combination with Reaction "A" allowed of the diagnosis of a large majority of pancreatic cases from the urine alone. This method, termed "B", depends on the fact that the preliminary treatment of the urine with perchloride of mercury interferes with the formation of crystals in cases of pancreatitis, but does not affect them in cases of cancer of the pancreas and other conditions which

which give rise to a positive "A" reaction.
This differentiating reaction is termed Reaction "B" by Dr. Cammidge. In it the filtered urine to the amount of 20 ccm. is thoroughly mixed with 10 ccm. of a saturated solution of perchloride of mercury, allowed to stand for a few minutes and then carefully filtered. To 10 cmm. of the filtered mixture 1 ccm. of strong hydrochloric acid is added, and the whole boiled for 10 minutes as in reaction "A". It is subsequently diluted with 5 ccm. of the mixed urine and perchloride solution and 10 ccm. of distilled water. The rest of the process is practically the same as in reaction "A". It will thus be seen that the author had evolved a method by which he was able to distinguish cases of acute and chronic pancreatitis from those due to carcinoma of the pancreas and cases of defective oxidation. Recognizing the small scope as an aid to diagnosis which this method proved he further established certain tests by which those cases of chronic pancreatitis, malignant disease of the pancreas, and diseases non-pancfeatic could be differentiated from one another and from acute pancreatitis. He found that on examining a number of urines with their crystalline formations and classifying them with the associated diseases of the pancreas, he obtained varying types of crystals, differing somewhat from one another ~~though~~ though having in all cases a general similarity as regards their form and arrangements. In malignant disease for example the crystals were as a rule coarser and

broader than those seen in simple inflammation and in the latter state the crystals from acute cases were on the whole finer than those seen in most instances in chronic inflammation. No hard and fast line separated one type from another and although to the experienced eye differences might be suggestive, no great reliance could be placed on this alone.
He next tried to differentiate the crystals of different diseases according to their solution time in sulphuric acid (33 per cent). It was at first thought that the time of solution would depend on the size of the crystal and although the coarser crystal usually took longer to ~~resolve~~ dissolve, this was not the invariable rule. By correlating the crystal and its solution time with the disease of the pancreas found he came to the conclusion that the time that the crystal took to dissolve depended rather on the character of the inflammatory reaction in the organ than on morphological alterations in the crystals themselves. Briefly stated, the following are the results he obtained:- (1). The acuter the inflammatory process the shorter the solution time, a few seconds to three-quarters of a minute being sufficient. (2). In chronic pancreatitis from one to one and a half (rarely two) minutes were required to effect solution. (3). The crystal from malignant disease as a rule took from three to five minutes to dissolve under the influence of the acid. The mean of several observations must be taken in order that any reliance may be placed on the solution time.

The crystals from non-pancreatic cases turn brown and dissolve in dilute sulphuric acid, in solution time most closely resembling those from chronic pancreatitis.

Phenyl-glucosazone crystals on the other hand in the same strength of acid, only slowly take on the brown colour and dissolve in about five minutes or more.

Dr. Cammidge summarises in the following way the results of his examination of urine by the before-mentioned reactions:- (1). If "A" and "B" prove negative, the pancreas is not the seat of disease. (2). If "A" proves positive and "B" negative, active inflammation of the pancreas is indicated; (a) the crystals obtained by the "A" method will dissolve in 33 per cent sulphuric acid in about half a minute, if the inflammation is acute; (b) if they take one to two minutes to dissolve the inflammation is chronic. 3. If "A" and "B" both prove positive, then there may be malignant disease of the pancreas; crystals as a rule taking from three to five minutes to disappear; (b) a pancreas damaged from past pancreatitis, the crystals here dissolving in from one to two minutes; (c) disease not associated with the pancreas when the crystals dissolve in about one minute.

The Critical Examination of the Reaction.

The above reaction useful as it seems to have proved to Dr. Cammidge in the diagnosis of pancreatic disease is yet difficult of acceptance as it appears on paper. It invites criticisms on many points, and in writing the paper it has been my endeavour to test

the reliability and worth of the observations upon which the reaction rests. Very shortly indeed, after the delivery of Dr. Cammidge's Lecture Drs. Ham and Cleland of the Pathological Institute, London Hospital, in an article in the British Medical Journal (Vol. 1, 1904, p.1347) published their experiences when the test was employed with normal urines and distilled water. They found that urines from patients, who to all appearances presented no evidence of pancreatic disease, gave a positive result, provided the solution was sufficiently concentrated. Yellow rosettes and sheaves crystallized out, after the liquid stood for about 24 hours. They came to the conclusion that the presence or absence of the crystals depended on the concentration of the fluid, and that the crystals themselves were due to a lead compound. To prove this they removed the lead in the solution by Ammonium Sulphide and filtration; the fluid was then heated to drive off the ammonia and sulphuretted hydrogen, the separated sulphur was filtered off, and the resulting filtrate yielded no crystals however concentrated they made the fluid. They also obtained crystals from distilled water, and concluded that in both cases they were due to the presence of lead compound. Dr. P.J. Cammidge replying to this criticism (p.1462 of the same volume) said that the technique of Ham and Cleland was at fault, and that the crystals ~~were~~ they obtained were in no respect identical with the pancreatic crystals and he further pointed out that the crystals he

obtained have a definite melting point and other characters clearly showing that they are an osazone derived from a carbo-hydrate body. He objects also to their method of removing lead salts as it introduces two factors which interfere with succeeding stages of "A" reaction. He thinks that their failure to find crystals was due rather to this method of removing lead salts than to the absence of the crystals themselves. In the same paper in a note by F.G. Bushnell (of Plymouth) the latter points out that he obtained crystals from normal urine but not from distilled water. He refers to a case of chronic interlobular pancreatitis in which he got a positive result from both "A" and "B", but makes no mention of solution time. On post-mortem examination no fat-necrosis was found. It would thus seem difficult to explain the liberation of glycerine.

Next in order of time is an article by O.C. Grumer of Leeds (same volume p.1516), in which he published 13 cases, including 3 cases of cancer of the pancreas which gave a negative result. Two cases of carcinoma round the bile-ducts yielded a positive reaction, as well as one case of cancer of the pancreas. In a case of gall-stones with subsequent chdecystotomy "A" gave a positive result, and there was no evidenc e of pancreatic disease in this case. The other cases gave negative results. Grumer concluded that the reaction is not obtainable in all urines and he found that crystals obtained from lead compounds had no resemblance to those from a positive pancreatic

reaction. I may add here that no mention is made regarding the concentration, or of the amount of fluid at the end of the reaction.

Dr. Cammidge replying to this in a note in Vol.11. of the British Medical Journal for 1904, p.43) states that he is unable to explain his results. He does not consider it surprising that some healthy urines yielded positive results, as on prolonged boiling of the urine with a mineral acid its reducing power is increased. He further states that those cases which gave a slight reaction can easily be distinguished from true positive pancreatic cases. In the same issue of the Journal, Drs. Ham and Cleland describe two forms of crystals,- one occurring as sharp needles in rosettes or less regular plumose tufts and due to a lead compound with phenyl-hydrazine; the other occurring when barium carbonate is used as an neutralizing agent, and differing from the first by occurring usually in rosettes and rarely as plumose tufts, and being obscured by yellow amorphous masses. They are smaller, though coarser, and less sharply pointed than the lead compounds. The solution time was not given. Replying to this article in a paper in the British Medical Journal, Vol.11, 1904, p.152 Dr. Cammidge says that 15-16 ccm. of fluid should be left at the end reaction. He does not say whether "A" or "B" but probably means the former. He seems inclined to attribute the finding of crystals in non-pancreatic cases to undue concentration of the liquid. In a paper in the Lancet of May 12th. 1904, Dr. Cammidge again

refers to the possibility of lead chloride passing through in the filtrate, unless neutralization and filtration be very carefully carried out, and believes that the crystals of Drs. Ham & Cleland were due to concentration of the liquid and separation of lead-chloride. So much for the general criticism which the publication of Dr. Cammidge's paper has evoked. I should like now to add my own opinions, based on numerous experiments carried out, according to the original directions, on distilled water, normal urines, diabetics and in some instances in cases of pancreatic disease (non-diabetic) either confirmed post-mortem or by surgical operation.

In the first place we may touch on his assumption regarding the excretion of glycerine or glycerose, on which the test is based. The working hypothesis is that glycerine separated by fat-necrosis is absorbed and excreted, in part at least, as glycerose. He quotes Catillon's statement that in dogs, 60-70% of glycerine given was excreted in the urine, but does not mention how much glycerine was given; as a matter of fact in many of Catillon's experiments, massive doses were given (see p.51 of his paper), such as 70 grms. or 10 grms. per kilo of the animal. In a man of ordinary weight this would correspond to 700 grms. Catillon points out that in man if a dose of less than 20 grms. is taken at one time, no glycerine at all appears in the urine, all being oxidised in the body; only when 20-30 grms. are taken as one dose is glycerine got from the urine (p.44).

Now in fat-necrosis theamount of glycerine liberated and absorbed per diem must be very small indeed, and one can hardly believe, that even in the case defective oxidation any of it could appear in the urine.
Even if glycerine were excreted as such it would not itself give any of the Cammidge crystals. I have proved this by numerous observations, and have found that glycerine boiled with hydrochloric acid yields no substance capable of forming an osazone body with phenyl-hydrazin. As a matter of fact when glycerine is heated with strong hydrochloric acid it yields chlorine substitution products (such as mono-acid di-chlor-hydrin) but this probably does not occur in the diluted solution I was using and in any case there is no evidence that these bodies form osazones.
If however glycerine diluted be boiled with nitric acid, I found that crystals could be obtained and that is not surprising seeing that glycerine is a body that yields many substances on treatment with an oxidising agent. For example, if glycerine is carefully oxidised with nitric acid or bromine water, glycerose is obtained, not a simple substance but a mixture of glyceric aldehyde ($CH_2OH.CHOH.COH$) and di-hydroxy - acetone ($CH_2OH.CO.CH_2OH$). Again, nitric acid may yield another body-glyceric acid ($CH_2OH.CHOH.CO_2H$). Under other conditions it yields glycollic acid ($CH_2OH.CO_2H$), oxalic acid ($CO_2H.CO_2H$) and carbonic dioxide (CO_2)

(See Perkin & Kipping's Organic Chemistry 1903, p.272). In this way we see that many bodies may result from the oxidation of glycerine. It is of course true that glycerose can form an osazone with phenylhydrazine, but it melts at 153° C. and any crystals I obtained melted at a temperature far higher than this. Dr. Cammidge makes free use of the term "melting point" but never informs us what it is. Having satisfied myself that glycerine as such would not, on boiling with hydrochloric acid yield a fluid which when neutralized could form an osazone, I proceeded to make a series of observations to see if the ingredients used in the reaction itself, could form crystals of the kind described.

I was struck with the frequency with which urines from apparently normal subjects yielded positive results, with definite crystalline masses and proceeded therefore to do control experiments with distilled water, everything else being carried out according to the Rules laid down. The first time this was done a negative result was obtained, but on repeating the experiment, I found that crystals could be obtained. That this was not a mere chance occurrence is borne out by the fact that I obtained them on six or seven occasions. Throughout I used hydrochloric acid and lead carbonate. When the fluid was examined first it never yielded crystals but when it was concentrated to 10 ccm. definite crystals in sheaves and rosettes made their appearance. They were coarser than crystals obtained from normal

urines and resisted the action of 33 per cent sulphuric acid. These most probably corresponded to the crystals found by Drs. Ham & Cleland.

These results naturally led me to suspect that it was the presence of lead-salts that was accountable for the crystalline deposit, and repeating my observations with normal urines I tested the filtrate after neutralization with lead carbonate by means of ammonium sulphide and obtained in every case a black precipitate of lead-sulphide. The presence of the lead is to be explained by the fact that lead chloride is not a very insoluble salt.

Owing to the fallacy introduced by this lead compound, I tried other re-agents, i.e. sulphuric acid ($\frac{1}{2}$ ccm. to 10 ccm. of urine) and strong acetic acid (1ccm. to 10 ccm. of urine): in the former case neutralization was done by means of lead carbonate- the very insoluble lead sulphate being formed; where acetic acid was used, sodic carbonate was employed to neutralize.

First, three specimens of distilled water were taken, 10 cm. each and boiled with 2 ccm. of glacial acetic acid for 10 minutes. The resulting fluid was neutralized with sodic carbonate and the rest of the reaction carried out in the ordinary way (boiling with sodium acetate and phenyl-hydrazine). However much the fluid was concentrated no crystals were obtained; e.g. each sample after first boiling left 10 ccm. of fluid and gave negative results; even if reduced to 7 and 2 ccm. no crystals appeared.

In the case of sulphuric acid, 10 ccm. of distilled water were boiled with 0.5 ccm. of strong sulphuric acid neutralized with lead carbonate and filtered. The filtrate was heated in the ordinary way with phenyl-hydrazine, and no deposit was found at the end of the reaction. On concentration to 7 or 8 ccm. large needle-shaped crystals were obtained. While working with normal and pathological urines in the early part of my observations none of the crystals obtained resembled the lead compound. I had followed Dr. Cammidge's rules with care. When however I concentrated the fluid a little at the end of the process, two kinds of crystals appeared,- one in small fine well-formed rosettes and sheaves, having no resemblance to the lead compound crystals, while the second kind easily seen with a ⅓" objective resembled the lead crystals, and were coarser and larger than those I mentioned first. These fine crystals were not always obtained at the end of the reaction but when wanting were generally obtained on concentrating the fluid. The crystals were obtained in both reaction "A" and "B" and differed but little in the two reactions. The solution time in 33 per cent sulphuric acid varied greatly, in some cases the crystals dissolving in 1 or 2 minutes, in other instances 15 minutes being needed to effect complete solution.

With a view to ascertaining the kind of crystals obtained when glycerine was given by the mouth observations were made on myself and others, after the

ingestion of glycerine. A dose of 1 oz. (about 28 grms.) was taken at night, and the morning urine collected. Reaction "A" showed numerous very well-formed crystals in rosettes lying amongst amorphous yellow debris. Reaction "B" gave a very scanty crystalline deposit, the needles being rather in sheaves than in rosettes. The crystals here differed little from those obtained in normal urines, where no glycerine had been artificially given. Special analysis of such urine (after ingesting glycerine) failed to reveal the presence of glycerine itself. This indicates that the taking of a moderate amount of glycerine has little effect on the crystals. This is further borne out by the following experiments- a lad of 10 years, a surgical case in the Glasgow Royal Infirmary was given 2 ozs. (about 60 grms.) of glycerine one evening. The urine was first carefully examined and gave a negative result with phenyl-hydrazine. The urine at this time was also tested by Reaction "A" and "B" that is, before glycerine had been administered. In reaction "A" small fine well-formed crystals were found, solution time 4 or 5 minutes, the quantity of fluid itself being 12 ccm. In reaction "B" well-formed crystals were obtained larger than those in "A", solution time in acid being 1½ minutes.

The day after 2 ozs. of glycerine were given, the urine yielded the following results:- (1) treated with phenyl-hydrazine, it gave no reaction: (2) in reaction "A" by Cammidge's method, very well-defined

crystals slightly larger than when glycerine was not taken were obtained, and in sheaves rather than in rosettes; (3) reaction "B" gave much the same results as reaction "A". It is clear from this that a dose of even 2 ozs. of glycerine had little influence upon the crop of crystals. No glycerine as such was detected in the urine.

In order to obtain if possible a urine free from crystals (which appeared to be rather a difficult thing to do) I examined the urine of guinea-pigs on an ordinary diet of cabbage and bruised turnips; the urine was collected over three days, 115 ccm. being obtained. As tested, it contained no sugar or albumen; it was very turbid from carbonates, and cleared up on adding acid,- Phenyl-hydrazine test was negative even when the deposit was extracted with alcohol. It was now subjected to reaction "A" and "B" with these results:- (1) "A" yielded a copious deposit which microscopically revealed a large number of crystals, well-shaped and very like phenyl-glucosazone. They appeared mainly in sheaves. (2) Reaction "B" gave small crystals like those of acid urate of soda, coarser than in "A" and darker inthe centre. In every case the guinea-pig's urine yielded this result. The urine was also boiled with acetic acid, and gave the same results, whether a neutralizing agent was used or not. It was found that before the reaction, the urine on boiling with Fehling's solution gave no reduction, until after prolonged boiling had been resorted to, when a greenish

opacity was observed in the blue-green fluid. After the end of the reaction the urine on boiling readily changed the Fehling to the ordinary brick-red ~~colour~~ colour with the ovlution of gas. From this one may conclude that the body which exists in the urine at first, is pretty certainly allied to the carbohydrate series, possibly being of the nature of dextrin or animal gum, which when treated with acids becomes of the nature of sugar and can reduce Fehling. The crystals obtained melted between 200° and 205° C and were therefore of the nature of a maltosazone or glucosazone; they had more of the morphological appearances of the latter.

Not only do guinea-pig's urines react in this manner but also many normal human urines though with them the crystals may not be so large or so abundant. This is probably determined by the diet. The possibility of error due to lead or other salts was eliminated here by using a method in which no salts were employed which could be a source of fallacy, ~~or~~ eg. by boiling with acetic acid and neutralizing with sodic carbonate, this salt produced sodium acetate and this is normally used in the phenyl-hydrazine test. In the case of human urines too, one seeks the source of the crystals in some pre-existing substance which has some relationship- perhaps not well-defined, to the sugar. It has been known for some time past that many urines have their reducing power increased on boiling with a mineral acid and various of these non sugar carbohydrates have been described.

Blumenthal gives short accounts of the following:-
(a) Reichardt described in diabetic patients a dextrin-like body, which gave a red-brown colour with iodine, and with prolonged heating gradually turned Fehling's solution green, and eventually a dark brown. Leube considered this body glycogen; he precipitated it by absolute alcohol, and boiled with 1 per cent sulphuric acid, when he produced dextrose. (b). Leo has described a lævo-rotatory body not fermentable even after boiling with dilute hydrochloric acid. It tasted distinctly sweet. (c) Rosin found in diabetic urines along with dextrose a body that could be isolated by special tests and concluded it to be animal gum. (d) Salkowski and Blumenthal have found in Pneumonia a fermentable urine which gave an osazone melting at 190°C or 10° below the osazone of grape-sugar. They considered the body to be glycosamine a derivation of glucose. (e) In some febrile and diabetic urines, osazones have been described with melting points ranging from 175° to 185°C (see Pathologie des Harnes, 1903, p.164). On looking over the above one is not surprised that urines after boiling with strong acids should yield crystalline osazones; it would be almost more remarkable if they did not.

Turning now to the differentiating feature betweem reactions "A" and "B", one can hardly regard Dr. Cammidge's statement save with grave scepticism for we are told that, presumably the same crystals derived from the same source, viz. the glycerine molecule in

fat-necrosis vary in character so much in different forms of pancreatic disease, that in acute pancreatitis they occur in reaction "A" and not in reaction "B" when a saturated solution of mercuric-chloride is first added to the sample, and that the same solution (viz. corrosive sublimate) in some mysterious way at one time inhibits the formation of crystals in reaction "B" and at another allows them to come through. Mercuric chloride certainly attains a new value if it can produce this remarkable and varying effect on the crystals. It seems that although the crystals are presumably the same in both cases, the mercuric solution is able to remove them in the one disease, and leave them over in the other. To my mind the only effect the mercury has is the well-known one of throwing down albuminous and colouring matter, as well as certain urinary salts, e.g. phosphates, urates etc. These might certainly carry down some of the osazone-forming bodies, but why should they do so consistently in acute pancreatitis, and not in malignant disease of the organ; I must confess that this statement of Dr. Cammidge's is a severe strain on one's credulity, and I cannot propose to offer any explanation of it. Then finally there is that part of the test which deals with the solubility of the crystals in 33 per cent sulphuric acid. I shall give a short resume of the points which I have already detailed (see p.47):- (1). He states that when solution time is about 1 minute, acute pancreatitis is indicated.

(2). When 2 or 3 minutes are needed, it points to chronic pancreatitis.

(3). When 4 or 5 minutes are required, malignant disease is indicated.

Although to all intent and purpose the same crystalline body is obtained in each case, for some inexplicable reason it behaves differently with the acid according to that morbid condition of the organ with which it is associated. The only explanation one could offer would be that the crystals in different cases vary in size, and hence in solution time, but this Dr. Cammidge himself points out is not the case. The solubility would appear to depend on something inherent to the crystal from any special form of disease and as to what that is, no one can hazard a guess. But as one of his critics pointedly remarks such a phenomenon as this would be analogous to obtaining phenyl-~~hydrazin~~ glucosazone crystals from urine, and then finding that they differed in solution time according as the glycosuria was hepatic, cerebral, pancreatic or alimentary in origin. Such a supposition would strike anyone as being exceedingly far-fetched and wanting in scientific support, and yet that is what Dr. Cammidge wishes us to accept regarding his so-called pancreatic crystals. My own experience is that the crystals from normal urines vary greatly as regards their solution time, some taking only a minute and a half to disappear, others persisting for fifteen minutes, and the coarser crystals

in general taking longer to dissolve than the finer ones. Some of them behave like crystals found by Dr. Cammidge while others like those characteristic of phenyl-glucosazone. Moreover I may add here that in the cases of pancreatic disease where I had the opportunity of testing the urine, the solution time was of no help, indeed was rather misleading. In one case which I saw at the Victoria Infirmary here, the crystals were obtained by reaction "A" and not by "B" they should therefore have been those due to active inflammation and ought to have dissolved in 1 to 2 minutes, but they took 4 to 5. In another case, proved post-mortem to be one of chronic inter-lobular pancreatitis affecting specially the body of the organ, crystals were obtained both in reaction "A" and "B" and dissolved in 1 minute; these crystals according to Dr. Cammidge, would point to a condition in which the pancreas was not affected.

Since I have mentioned these cases I should like to cite a few more of interest where I have performed this re-action:-

(1). Jane M, 55, Single, in Victoria Infirmary, suffering from cholelithiasis with marked jaundice.
Reaction "A" - scanty badly-formed crystal: solution time 4 or 5 minutes.
Reaction "B"- scanty positive results (rosettes rather than sheaves). Solution in over 5 minutes.
Maliganat disease of pancreas would be indicated here; no evidence on operation.

(2). Mrs. M., carcinoma of head of pancreas.

Reaction "A" scanty badly-formed crystals in sheaves and rosettes, solution in 1 minute.
Reaction "B"- the same. (rosettes rather than sheaves) Solution 1½ to 2 minutes. This suggests a damaged pancreas from old mischief, the actual lesion was a cancer. On a second occasion this urine gave negative results ("A" and "B").
(3). Pancreatic diabetes in a male, Reaction "A" after the urine had been freed from sugar by fermentation yielded well-marked acicular crystal in rosettes, much finer than those got from normal urine. Solution time was ½ to 1 minute. Reaction "B" very scanty (small rosettes); solution time 1 to 2 minutes. This case I saw in the Royal Infirmary, Glasgow, it being one where at the suggestion of Dr. Allan, an attempt was made to graft a dog's pancreas on to the abdominal parietes of the patient. The patient died in coma.
(4). Woman, middle-aged, with cholelethiasis; Ward 111, Western Infirmary. The urine contained bile but no sugar or albumen.
Reaction "A"- well-formed crystals obscured by granular debris; solution time 3 or 4 minutes.
Reaction "B"- copious deposit of fine-needle-like crystals (larger than "A"); solution in 3 minutes and over. This would indicate malignant disease of the pancreas.
To show the readiness with which the test reacts with normal urines, I quote a few cases:- (5). H: male, 23, good healthy general health: reaction "A"

positive showing short well-formed rosettes (abundant) and fewer sheaves; solution time from 1 to 1½ minutes. Reaction "B"- positive, distinct and more marked than in "A": solution-time: in 5 minutes crystal still distinct; fully dissolved in 15 minutes. There was really no evidence here of pancreatic disease. (6). P.J., male, 17, ordinary good health. Reaction "A" well-formed crystals in rosettes rather than sheaves. Solution-time - 2 minutes (incomplete): complete in 5 minutes. Reaction "B"- a few decolourized sheaves and a few rosettes coloured. Doubtful reaction: solution-time not taken.
(7). J.T., male, 25, ordinary good health: fasting. One ounce of glycerine taken at night, morning urine examined. Albumen and sugar absent. Reaction "A" well-formed crystals in sheaves and rosettes: abundant granular debris. Reaction "B"- very scanty crystalline formation of a few sheaves; no rosettes. That these crystals were not due to the glycerine is found by the fact that better crystals still were got when no glycerine had been given at all.
Numerous other observations could be recorded, but it would subserve no special object, enough having been said to indicate that crystals may be obtained from normal urines. The constant repetition of isolated observations is uninteresting and unconvincing, and I shall therefore focus my results in certain general conclusions.

1. The test as a diagnostic indication for cases of pancreatic disease has not proved itself of any real

value whatever, either in my hands or those of other observers who have recorded their results. The fallacy lies chiefly in this, that although pancreatic cases as a rule yield positive results as far as the appearances of crystals is concerned, many cases non-pancreatic do the same; and further that where, in genuine pancreatic cases, conclusions have been drawn as to the precise lesion, from the reactions "A" or "B", and the solution-time, these conclusions have frequently been found to be quite misleading. For example, the reaction may point to the presence of a chronic pancreatitis, where in reality a malignant tumour of the head of the gland is the lesion that exists.

2. One is struck by the large number of urines, normal and morbid (I do not refer here to pancreatic disease), in which a positive result varying in degree is obtained. In some cases the crystals are small, ill-formed and indistinct; in others clear and striking. It has even been found that urine from the same (normal) person can yield varying results:- negative, equivocal or well-marked as the case might be.

3. The occurrence of crystals is largely affected by the degree of concentration of the fluid left at the end of the process, although concentration is not a necessary factor for their production. It is particularly the case that concentration leads to error when the reactions are carried out according to Dr. Cammidge's directions,- the error here being due to the presence of lead-salts. In many of my observations however, this fallacy was obviated by my method,

of using no lead compounds, and it was in these cases that I noted how important a bearing concentration had on the test. Concentration was no doubt necessitated in some cases by the small amount of crystal-yielding substance present in the urine, crystals only appearing when it existed in a certain percentage.

4. It appears to me that there are at all events two sources for these crystals, one being genuine carbohydrate or at least osazone-forming substance, the other being inorganic material e.g. lead chloride. I cannot agree with Drs. Ham & Cleland that the crystals are generally due to the latter; I consider the presence of lead-salts a minor cause of fallacy, as, when controls are done with distilled water, no crystals are obtained till the fluid is concentrated below 10 ccm. In all cases however, in which Cammidge's method is followed, lead salt comes through, however carefully the filtration is carried out.

5. The common source of the crystals, is in my opinion, some carbohydrate body of the nature of dextrin or animal-gum already existing in the urine, and inverted into a true sugar, on boiling with mineral acid, or even strong acetic acid. This is borne out by the much greater reducing power of such urines after boiling, as tested with Fehlings solution. On doing the fermentation test a very small amount of gas forms, but this can be easily accounted for by the small total amount of sugar

present, and the solubility of CO_2 in the fluid.

6. In the guinea-pig's urine particularly, crystals were obtained in every case, and no concentration was required. The fallacy of lead-salts was eliminated by using acetic acid and sodic carbonate as a neutralizer, and the form of those crystals very closely resembled that of phenyl-glucosazone crystals; they melted at practically the same temperature. I regard these as genuine sugar-produced crystals, their source being the carbohydrate material in which the food of the guinea-pig is rich.

To sum up, while one cannot deny that these crystals occur in disease of the pancreas at the same time one meets with crystals to all intents and purposes identical with those of pancreatic cases, in normal urines and in urines from various morbid conditions non-pancreatic. The reaction may often be slight, but not infrequently is marked, and as there is no satisfactory means of distinguishing between the two varieties of crystals (pancreatic and non-pancreatic), one is obliged, albeit reluctantly to conclude that the test is not a reliable one, judged by modern clinical standards, and in hands other than those of its originator, has proved not only equivocal but even misleading.

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